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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,963	TONGE ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-28,41-43 and 51-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-28,41-43 and 51-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *14 August 2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 26-28, 41-43 and 51-53 are presented for examination.

Applicant's Amendment and Information Disclosure Statements (IDS) filed August 14, 2009 have each been received and entered into the present application.

Claims 26-28, 41-43 and 51-53 are pending and under examination. Claims 29-40 and 44-50 are cancelled. Claims 26-28 and 41-43 are amended. Claims 51-53 are newly added.

Applicant's arguments, filed August 14, 2009, have been fully considered but they are not deemed to be persuasive. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Applicant's Information Disclosure Statement filed August 14, 2009

Applicant has filed two Information Disclosure Statements on August 14, 2009. The IDS filed August 14, 2009 containing the references designated as Cite Nos. AA-AH has been lined out since these references have already been considered pursuant to the initialed IDS dated May 20, 2009. The second IDS filed August 14, 2009 electronically containing citations to the James et al. and Fizazi et al. references is not a proper submission in accordance with MPEP §609 and 37 C.F.R. 1.98. The Information Disclosure Statement fails to comply with 37 C.F.R. 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. Applicant's information disclosure

statement electronically filed August 14, 2009 has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 26-28, 41-43 and 51-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bradbury et al. (U.S. Patent No. 5,866,568; 1999) in view of Hsu et al. ("ET-1 Expression and Growth Inhibition of Prostate Cancer Cells: A Retinoid Target with Novel Specificity", *Cancer Research*, 1998; 58:4817-4822) and Nelson et al. ("Identification of Endothelin-1 in the Pathophysiology of Metastatic Adenocarcinoma of the Prostate", *Nature Medicine*, 1995; 1(9):944-949), each already of record, for the reasons set forth at p.7-11 of the previous Office Action dated May 20, 2009, of which said reasons are herein incorporated by reference.

Newly added claims 51-53 are properly included in the present rejection because Bradbury et al. clearly discloses that the compounds taught therein are administered for therapeutic purposes to warm-

blooded animals, including man, requiring such treatment in the form of a pharmaceutical composition (col.17, l.19-23).

Response to Applicant's Arguments

Applicant traverses the instant rejection, stating that there is no motivation to select the instantly claimed compound from the 70 compounds disclosed in Bradbury et al. and then to test it in prostate cancer, which is allegedly not listed as a therapeutic indication by Bradbury et al. Applicant opines that there is no reason one would have to combine the teachings of Bradbury et al., Hsu et al. and Nelson et al. except via impermissible hindsight reasoning. Applicant asserts that there are two types of endothelin receptors, i.e., ET_A and ET_B, wherein the B receptor is allegedly involved in apoptotic signaling, whereas the ET_A receptor is the one that is important in managing certain cancers. Applicant references the article entitled "Prostate Cancer: New Endothelin-A Receptor Antagonist Prolongs Survival" published in 2009 to show that other endothelin antagonists with activity at both the endothelin-A and endothelin-B receptors do not demonstrate the same degree of improvement in overall survival as antagonists with activity only at endothelin-A.

Applicant's traversal has been fully and carefully considered, but fails to be persuasive.

Firstly, Applicant's remarks regarding the lack of motivation to select the claimed compound from those listed in Bradbury et al. and to then use said compound in prostate cancer are puzzling because they seem to completely disregard the rationale and reasoning provided in the rejection set forth at p.7-11 of the previous Office Action. Applicant posits several questions at p.8 of the Remarks that narrowly interpret the prior art in a vacuum without considering the reasons as to why they were combined in the context of the instant rejection. In addition, these same questions improperly generalize the teachings of the cited references to ostensibly support Applicant's position that the discovery of the prior art cited by the Examiner is tantamount to finding a needle in a haystack such that the references could then only be

combined using impermissible hindsight. This argument is, and will continue to be, unpersuasive in view of the extensive reasons and clear statements of motivation provided in the previous Office Action, which will not be repeated herein so as not to burden the record.

Contrary to Applicant's allegations that there is no reason to combine the cited references, there is clear motivation to combine the cited prior art because Bradbury et al. teaches heterocyclic compounds that function as endothelin-1 receptor antagonists, including the specifically named compound N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide, and are useful for treating diseases or medical conditions in which elevated or abnormal levels of endothelin play a significant causative role, including certain cancers. Hsu et al. teaches that ET-1 is an important growth stimulator that both regulates and promotes tumor growth in prostate cancer and that blockage of ET-1 is capable of suppressing both tumor growth (i.e., tumors in a non-metastatic state) and tumor metastasis (i.e., tumors in a metastatic state). The skilled artisan would have been clearly motivated to use the compound disclosed by Bradbury et al. because the compound was known in the prior art as an ET-1 inhibitor useful for treating cancers and, as evidenced by Hsu et al., ET-1 was known to promote the growth and metastasis of prostate tumors. These are unequivocal teachings that support the concept of using the compound(s) of Bradbury et al., *already known to be useful for treating cancers* (which is a teaching that Applicant conspicuously refuses to acknowledge), for the treatment of, in particular, prostate cancer, absent factual evidence to the contrary.

The fact that Bradbury et al. may disclose other compounds within the four corners of the reference is irrelevant because each of the compounds is disclosed alternatively as each being functional to antagonize ET-1 receptors and, therefore, would have been clearly useful for the therapeutic indications therein. The motivation to select any one of the compounds out of the genus disclosed in Bradbury et al. is clearly derived from the disclosure of each compound as an alternative embodiment, each of which may be individually selected and each of which is disclosed as equally operative to function as an ET-1

receptor antagonist effective to treat, *inter alia*, cancers. These facts clearly foreclose the argument that there is no reason to particularly select the instantly claimed compound from the disclosure of Bradbury et al. for use in treating cancer, since Bradbury et al. alone provides an explicit correlation between the ET-1 receptor antagonists therein and their therapeutic efficacy in treating cancers *per se*.

In view of these facts, it is clear that Applicant's insistence that the Examiner's rationale is grounded in hindsight analysis is clearly unpersuasive. Applicant is reminded that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. However, so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Considering the fact that the present rejection under 35 U.S.C. 103(a) relies solely on the knowledge and motivation that was generally available to one of ordinary skill in the art at the time of the invention (as clearly elucidated *supra*, as well as in the previous Office Action) and does not improperly rely upon Applicant's disclosure, the assertion that the present rejection is made with impermissible hindsight reconstruction is, and will remain, unpersuasive.

Secondly, Applicant's attempts to argue that, because there are two types of endothelin receptors, ET_A and ET_B (wherein the endothelin-B receptor is allegedly involved in apoptotic signaling and the ET_A receptor is important in managing certain cancers), it would not have been predicted from the prior art that the compound of Bradbury et al. would have been effective in treating prostate cancer because the reference does not teach that the compound has activity at the endothelin-A receptor. This is unpersuasive for several reasons. Firstly, Bradbury et al. already acknowledges that the compounds disclosed therein are both functional antagonists of ET-1 receptors *and* that they are also therapeutically effective for the treatment of certain cancers. The very teaching that such compounds are useful for the treatment of cancers clearly indicates that Bradbury et al. would not employed such compounds for the purpose of

interfering with the apoptotic process because, as Applicant has even admitted on the record, interfering with or stopping the process of apoptosis would have prevented normal cell death and promoted tumor growth (i.e., which would have been an undesirable property of an oncology compound). Thus, it is reasonable to infer from what Applicant has established as the state of the art and what was known from the cited prior art that the endothelin antagonists of Bradbury et al. do not function as selective antagonists of the ET_B receptor (which is the receptor correlated to apoptotic pathways) if they are useful in treating cancers. Secondly, Hsu et al. explicitly teaches that ET-1 is a growth stimulator in various cancers, including prostate cancer, by regulating and promoting tumor growth. Thus, the references provide a clear basis to conclude that a compound functional to inhibit ET-1 would have been reasonably expected to successfully treat prostate cancer by reducing the levels of the prostate tumor stimulator ET-1, absent factual evidence to the contrary. The cited references clearly provide a reason and, notably, a reasonable expectation of success in predictably effecting the treatment of prostate cancer, to combine the two references based on the common ET-1 function and without restriction as to the subtype of endothelin receptor (i.e., either A or B).

The fact that some endothelin-A antagonists have measurable and undesirable endothelin-B properties drifts away from the issue. What is at issue in the present case is whether the prior art provides a *prima facie* case of obviousness as to why one of skill in the art would have employed the compound of Bradbury et al., disclosed as an ET-1 receptor antagonist, for the treatment of prostate cancer, which, for the reasons above and those already of record, it does. The teachings of the prior art clearly correlate the use of a known ET-1 antagonist, already disclosed as being useful for treating cancer, for the purpose of specifically treating prostate cancer, whose growth and metastasis is known to be promoted by the growth stimulator ET-1. In other words, the question of whether the compound is an ET_A or ET_B antagonist is clearly a peripheral issue because the prior art provides an unambiguous reason to employ the instantly

claimed compound for treating prostate cancer outside of its function as an antagonist of either the endothelin-A or endothelin-B receptor subtype.

Thirdly, and lastly, Applicant cites to the article entitled "Prostate Cancer: New Endothelin-A Receptor Antagonist Prolongs Survival" published in 2009 to show that other endothelin antagonists with activity at both the endothelin-A and endothelin-B receptors do not demonstrate the same degree of improvement in overall survival as antagonists with activity only at endothelin-A. The citation to this reference is an attempt to underscore Applicant's position that one of skill in the art would not have used a compound for treating cancer that had activity at the ET_B receptor. However, the *prima facie* case of obviousness is not founded on the concept of using an ET_B receptor (or even a mixed ET_A and ET_B receptor) for the treatment of prostate cancer, but rather to use an ET-1 receptor antagonist already known to have anti-cancer activity to treat a specific cancer whose growth is known to be stimulated by ET-1 (i.e., prostate cancer). In addition, Applicant has provided no evidence tending to support his apparent position that the art recognized the instantly claimed compound as an ET_B antagonist such that it would not have been obvious (i.e., that the art somehow taught away from its use) to use such a compound as an anticancer agent because of its pro-apoptotic capabilities. Accordingly, these arguments regarding the function of antagonists at the ET_A and ET_B receptors are unimpressive in establishing nonobviousness of the instantly claimed subject matter in view of the cited prior art.

For these reasons *supra*, and those previously made of record at p.7-11 of the Office Action dated May 20, 2009, rejection of claims 26-28, 41-43 and 51-53 is proper.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163

USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 26-28, 41-43 and 51-53 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 42-44 of U.S. Patent Application No. 11/720,001 in view of Bradbury et al. (U.S. Patent No. 5,866,568; 1999), Hsu et al. ("ET-1 Expression and Growth Inhibition of Prostate Cancer Cells: A Retinoid Target with Novel Specificity", *Cancer Research*, 1998; 58:4817-4822) And Nelson et al. ("Identification of Endothelin-1 in the Pathophysiology of Metastatic Adenocarcinoma of the Prostate", *Nature Medicine*, 1995; 1(9):944-949), each already of record, for the reasons of record set forth at p.13-18 of the previous Office Action dated May 20, 2009, of which said reasons are herein incorporated by reference.

Newly added claims 51-53 are properly included in the present rejection because the copending claims clearly provide for the treatment of a warm-blooded animal such as man.

Applicant requests that the instant provisional rejection be held in abeyance until the present application is considered allowable and this is the only issue that remains.

In view of the fact that the present application is not in condition for allowance at this time, and further in view of the fact that Applicant has not filed a Terminal Disclaimer, the rejection remains proper and is hereby maintained.

Double Patenting (New Grounds of Rejection)

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual

or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 26-28, 41-43 and 51-53 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 42-44 of U.S. Patent Application No. 12/483,821 in view of Bradbury et al. (U.S. Patent No. 5,866,568; 1999), Hsu et al. ("ET-1 Expression and Growth Inhibition of Prostate Cancer Cells: A Retinoid Target with Novel Specificity", *Cancer Research*, 1998; 58:4817-4822) and Nelson et al. ("Identification of Endothelin-1 in the Pathophysiology of Metastatic Adenocarcinoma of the Prostate", *Nature Medicine*, 1995; 1(9):944-949).

Note that the instant rejection is newly applied but does not constitute a rejection that prevents the finality of the instant office action because the copending '821 was filed by Applicant after the non-final rejection dated May 20, 2009 and, therefore, could not have been applied in the earlier action.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the cited application are not considered patentably distinct from each other because the pending claims are anticipated and/or rendered obvious by the copending claims.

The copending claims clearly provide for the treatment of cancer, specifically prostate cancer, in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a combination of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide and an anti-mitotic cytotoxic agent (copending claims 42-44).

The copending claims fail to teach the treatment of either metastatic (claim 41) or non-metastatic prostate cancer (claim 42), that the cancer is producing bone metastases (claim 43) or that the disclosed compound is effective for inducing differentiation of a cancerous cell (claim 27) or inducing apoptosis in a cancerous cell (claim 28).

Bradbury et al. teaches heterocyclic compounds that possess endothelin receptor antagonist activity and are useful for the treatment of diseases or medical conditions in which elevated or abnormal levels of endothelin play a significant causative role (abstract). Bradbury et al. teaches that compounds of particular interest include various exemplified embodiments, such as, *inter alia*, the compound of Example 36 (col.11, l.3-10), i.e., N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide (col.41, Ex.36) and further demonstrates that the compounds of the disclosure show inhibition of endothelin-1 (i.e., function as an endothelin-1 receptor antagonist by inhibiting binding of endothelin-1 to its receptors) (col.15, l.14-64).

Hsu et al. teaches that endothelin-1 is a potent vasoconstrictor and an important growth stimulator in various cancers, including prostate cancer, which suggests that blockage of ET-1 production is capable of suppressing tumor growth and metastasis (abstract). Hsu et al. teaches that a 2.6 times higher level of ET-1 was found in the plasma of patients with advanced prostate cancer as compared with healthy males, which suggests that ET-1 regulates and promotes prostate tumor growth (col.1, para.2, p.4817).

Nelson et al. teaches that advanced, hormone-refractory prostate cancer is characterized by painful osteoblastic bone metastases (abstract). Nelson et al. discloses that endothelin-1 (ET-1) is a normal ejaculate protein that also stimulate osteoblasts and teaches that the ectopic secretion of ET-1 may be a mediator of the osteoblastic response of bone to metastatic prostate cancer (abstract) because osteoblasts have high-affinity ET-1 receptors, acts on a number of pathways and inhibits bone resorption and motility of osteoclasts, which enhances the emergence of osteoblastic lesions (col.1-2, p.947). Nelson et al. states that ET-1 may have a significant role in the formation of osteosclerotic bone lesions

and suggests that, for endothelin-secreting phenotypes of advanced prostate cancer, the use of therapies directed against endothelin is both rational and strategic (col.2, para.2-3, p.947).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to treat non-metastatic or metastatic prostate cancer or to reduce the abnormal proliferation of prostate cancer cells using the copending composition because (1) Bradbury et al. teaches that the compound N-(3-methoxy-5-methyl-pyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]-phenyl)-pyridine-3-sulphonamide functions as an ET-1 receptor antagonist via inhibiting binding of ET-1 to its receptors and is useful for treating diseases or medical conditions in which elevated or abnormal levels of endothelin play a significant causative role, including certain cancers and (2) Hsu et al. teaches that ET-1 is an important growth stimulator that both regulates and promotes tumor growth in prostate cancer and that blockage of ET-1 is capable of suppressing both tumor growth (such as, e.g., tumors in a non-metastatic state) and tumor metastasis (i.e., tumors in a metastatic state). Such a person would have been motivated to do so because the N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]-phenyl)-pyridine-3-sulphonamide compound of the copending claims functions as an inhibitor of ET-1 as evidenced by Bradbury et al. and, as evidenced by Hsu et al., ET-1 is known to regulate and promote prostate tumor growth and metastasis. Thus, the skilled artisan would have had a reasonable expectation of successfully treating non-metastatic or metastatic prostate cancer using the composition of the copending claims because the sulphonamide compound of the copending composition was known in the prior art as an ET-1 inhibitor and ET-1 was known to promote the growth and metastasis of prostate tumors.

Furthermore, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to use the copending composition to treat prostate cancer that is also producing bone metastases because (1) Bradbury et al. teaches that the compound N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide functions as an ET-1 receptor antagonist via inhibiting binding of ET-1 to its receptors and is useful for treating diseases or medical conditions in

which elevated or abnormal levels of endothelin play a significant causative role, including certain cancers and (2) ET-1 is not only a potent stimulator of tumor growth and metastasis in prostate cancer (as evidenced by Hsu et al.), but is also a stimulator of osteoblasts and is known to contribute to the osteoblastic response of bone to metastatic prostate cancer to form painful osteoblastic bone metastases, as evidenced by Nelson et al. Such a person would have been motivated to do so not only to inhibit the function of ET-1 in promoting both prostate tumor growth and metastases, but also to inhibit the function of ET-1 in stimulating osteoblasts that form painful osteoblastic bone metastases in advanced stages of prostate cancer.

Though the effects in inducing differentiation or apoptosis in a cancerous cell, wherein the cancerous cell is a prostate cancer cell (claims 27-28) are not explicitly noted in the copending claims, it is noted that the teaching of the identical manner of administration of the identical compound to that presently claimed in the same host in a therapeutically effective amount for treating the identical disorder must necessarily possess such differentiation-inducing or apoptosis-inducing effects, even though such properties may not have been appreciated by the patentee(s) at the time of the invention. Products of identical chemical composition cannot exert mutually exclusive properties when administered under the same circumstances or, in the present case, the same host in the same amount. Please see MPEP §2112.

In re Best (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe includes functions and/or properties that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the Applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the newly cited function and/or property at the time of invention, so long as the function and/or property can be demonstrated to be reasonably expected to be present. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67

USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention"). Note that, even though *Toro* was decided in the context of inherent anticipation, considerations of inherent teachings arise both in the context of anticipation and obviousness (see, e.g., *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) or *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983) and MPEP §2112).

Accordingly, rejection of claims 26-28, 41-43 and 51-53 is proper over claims 42-44 of U.S. Patent Application No. 12/483,821 as claiming obvious and unpatentable variants thereof.

Conclusion

Rejection of claims 26-28, 41-43 and 51-53 is proper.

No claims of the present application are allowed.

Applicant's amendment to the claims and/or amendments to his set of copending applications necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the

mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

November 9, 2009

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614